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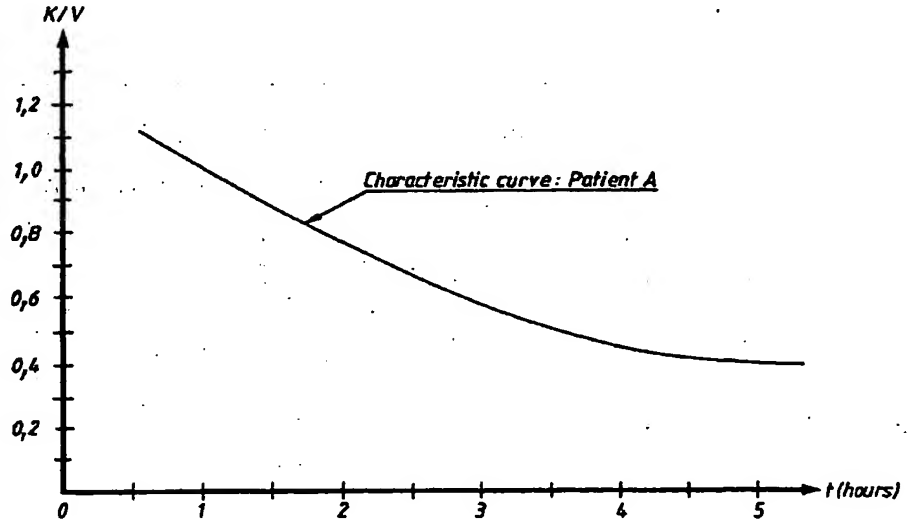
(54) Title: METHOD AND SYSTEM FOR PREVENTING INTRADIALYTIC SYMPTOMATOLOGY



(57) Abstract

A method and system for profiling the efficiency of a dialysis treatment, whereby a patient is exposed for dialysis by passing the patient's blood in an extracorporeal circuit through a dialyzer. The effluent fluid from the dialyzer (or hemofilter) is analyzed for the concentration of urea, by a urea monitor, or any other marker molecule. The dialysis treatment is carried out as efficient as possible until a limit value is reached indicative of the fact that the patient is approaching a break-down point, such as disequilibrium syndrome or hypotension. Thence, the efficiency of the dialysis treatment is profiled so that the patient will not reach his break-down point. The efficiency can be decreased according to an exponential curve. Alternatively, the urea monitor controls the efficiency. The limit value is determined by urea monitor measurement, or by predetermined patient data in a characteristic patient break-down curve. One indication is that the total removed urea (TRU) is determined and when the TRU reaches a predetermined value, it is an indication of reaching said limit value.

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TITLE: METHOD AND SYSTEM FOR PREVENTING INTRADIALYTIC SYMPTOMATOLOGY

FIELD OF INVENTION

The present invention relates to the field of preventing intradialytic symptomatology during dialysis, such as hemodialysis, hemodiafiltration or hemofiltration, continuous as well as acute therapy.

STATE OF THE ART

One intradialytic symptom is the disequilibrium syndrome first described in 1961. The disequilibrium syndrome is a set of systemic and neurologic symptoms that can occur either during or soon after dialysis. Early symptoms are nausea, vomiting, restlessness and headache and followed by seizures, obtundation and coma. Some believe that the cause is related to an acute increase in brain water content, while others believe that acute changes in pH of the cerebrospinal fluid during dialysis is a cause. The problem is greater when acute patients with very high plasma urea nitrogen values are subject to too efficient a dialysis.

The treatment of mild symptoms is to decrease the efficiency of the solute removal and pH changes for instance by reducing the blood flow. Hypertonic NaCl or glucose can be administered.

At more severe symptoms, the dialysis session should be stopped. Intravenous mannitol may be of benefit.

The disequilibrium syndrome can be avoided by using high NaCl concentration of at least 140 mmol/l and by using

glucose of at least 200 mg/dl. Decreasing sodium dialysis solution during dialysis treatment has also been suggested.

Another common intradialytic complication is symptomatic hypotension which normally is related to excessively rapid decrease in the blood volume during dialysis. Today most dialysis machines use volume control of ultrafiltration, which is a method aiding in preventing symptomatic hypotension. Other methods are profiling of sodium, low temperature, switch from acetate to bicarbonate etc.

Furthermore, ultrafiltration below the patient's dry weight may result in symptomatic hypotension associated with for instance cramps, dizziness, malaise and a washed-out feeling.

The present invention aims at solving these and related intradialytic complications in dialysis.

Biofeedback is a subject being investigated by many researchers. One example is US-A-4,469,593 disclosing a blood purification apparatus including a hematocrit measurement apparatus. The hematocrit value is used for controlling a negative ultrafiltration pressure at the dialysate side of a dialyzer for maintaining the hematocrit value constant or according to a pre-defined profile. Also the conductivity of the blood or plasma is used for establishing an upper limit for sodium while the hematocrit value controls both the addition of replacement fluid and increases the sodium concentration in a hemofiltration apparatus. Finally, the oncotic pressure is also used for biofeedback.

WO 94/08641 discloses an on-line real time urea sensor used for measuring the urea concentration in the effluent from the dialyzer. The system establishes two exponential fits of the urea concentration, with an early fit during the first 30 minutes and a late fit during the flowing treatment time. By obtaining an initial BUN-value, the Kt/V or SRI (solute removal index) can be calculated and projected to the intended time. In this way, the efficiency of the treatment can be measured on line. It is stated that the efficiency

decreases all the time during the treatment time, although presumably more slowly at the end. It is also stated that a deviation from a projected Kt/V can be used for troubleshooting.

WO 95/32010 discloses a method of determining the optimum blood flow (as measured by pump speed) for obtaining the most efficient dialysis. It is observed that the efficiency or clearance of the dialyzer is dependent on blood flow rate (and dialysis flow rate, as well as temperature etc.). However, above a predetermined blood flow, the efficiency of the dialyzer decreases again. There are several factors for this phenomenon, one of which being fistula recirculation. According to WO 95/32010, the efficiency of the dialyzer is determined at different blood flows, for example in increments of 50 ml/min, and the blood flow at maximum clearance is used. The maximum blood flow is determined at the start of each treatment. If this maximum blood flow declines after a number of weeks or days, it can be a sign of fistula malfunction. In this specification, a urea sensor is used for assessing the efficiency of the treatment at the start.

DISCLOSURE OF THE INVENTION

The object of the present invention is to suggest a method and apparatus for performing dialysis or a similar treatment as fast as possible while minimizing the inconvenience to the patient.

It has been found that each patient has a characteristic curve for maximum tolerated treatment efficiency versus time. According to the invention, the treatment is performed as efficiently as possible until said curve is reached or approached and thereafter, the treatment efficiency is decreased so that said curve is never reached.

In an alternative embodiment of the invention, the dialysis treatment is preceded by isolated ultrafiltration. The dialysis treatment is performed with high efficiency until said characteristic curve is approached. The continued treatment is

performed with decreasing efficiency so that said curve is never reached.

A more detailed definition of the invention can be found in the following claims.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be described in more detail with reference to certain embodiments shown in the drawings, wherein:

Fig. 1 is a diagram showing a typical characteristic curve for a specific patient.

Fig. 2 is a diagram showing an efficiency curve.

Fig. 3 is a typical urea sensor output curve.

Fig. 4 is a schematic diagram of a dialysis machine incorporating the present invention.

Fig. 5 is a schematic diagram of a hemodiafiltration machine incorporating the present invention.

Fig. 6 is a schematic diagram of a hemofiltration machine incorporating the present invention.

Fig. 7 is a schematic diagram of another hemofiltration machine incorporating the present invention.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENT

According to the present invention, it has been found that a specific patient being exposed to efficient dialysis, for example with the target of Kt/V = 2.0 or higher, will risk to become symptomatic if the efficiency is too high and the dialysis time is too short. For example, a patient prescribed at Kt/V = 2.0 during 4 hours will need an efficiency of K/V = 0.5, which could result in the collapse of this patient. However, if the time was increased to 5 hours and, consequently, the efficiency was decreased to K/V = 0.4, then the patient could stand the treatment without collapse or reaching his breakpoint. Other patients may become symptomatic

even at lower Kt/V and efficiencies and the above figures are only given as an example.

It has been found that a specific patient has a characteristic curve as shown in Fig. 1. If the curve is exceeded, the patient will break down. As appears from Fig. 1, it would not be possible to reach the goal of Kt/V = 2.0 in 4 hours without passing the characteristic curve.

Probably, the characteristic curve is in fact a series of curves depending on other factors of the dialysis, such as ultrafiltration rate, start BUN, sodium concentration or profiling, bicarbonate concentration, as well as psychological or physiological factors such as illness or depression etc.

According to the present invention, it is suggested to profile the efficiency of the treatment according to a specific profile adapted to the patient. Such a profile could involve starting with as high efficiency as possible, for example K/V = 0.6 during one hour, then decreasing the efficiency stepwise to K/V = 0.5 during the second hour, K/V = 0.4 during the third hour and K/V = 0.3 during the last hour, which would result in Kt/V = 1.8 during four hours. By on line measurement of the efficiency by a urea monitor, it can be monitored that the desired efficiency is obtained in reality and the efficiency can be adjusted automatically to follow the desired profile.

In a preferred embodiment, the efficiency of the treatment is as high as possible at the start, until a limit value is reached, which is indicative to the fact that the patient is approaching his characteristic curve and cannot withstand high efficiency dialysis any longer. After the limit value has been reached, the efficiency is changed according to a predetermined curve. When the desired goal has been obtained, the treatment is terminated.

The limit value can be determined in several ways. It can be determined empirically so that the characteristic curve of a specific patient is determined by exposing him to

different dialysis efficiencies and monitoring his data. In this way, the limit value can be established by looking into the curve.

It is often not possible to expose a specific patient to such different dialysis efficiencies and driving the patient to disequilibrium conditions just to obtain a characteristic curve.

Another approach is to monitor the removal of urea by the urea monitor and when a predetermined amount of urea has been removed, the limit value has been reached.

This amount of urea is obtained by integrating the value obtained by the urea sensor, which are concentration values. If it can be assumed that the dialysis fluid flow is constant, the total removed urea (TRU) is the integral of the concentration curve. Otherwise, the concentration curve is multiplied by the volume flow of the dialysis fluid at any time and then integrated to obtain the mass of urea removed.

The amount of urea can be a predetermined proportion of the urea production between the dialysis sessions, for example 50% - 90%, or more preferable 65% - 80%, for example 75%, or the urea generated between the dialysis treatments. Often it can be assumed that the urea generation is fairly constant during a short time span such as a week. Formulas are known for the urea generation for hemodialysis patients, which can be used for initial determination of this amount of urea removed for reaching the disequilibrium limit value.

Another approach to determine when the patient is close to his characteristic curve would be to monitor when the concentration in the blood reaches a predetermined lower value, which is indicative of reaching said limit value. It is more convenient to monitor the concentration in the dialysis fluid, which, however, is a mirror of the concentration in the blood.

After reaching said limit value, the efficiency is changed. One approach is to decrease the efficiency step-wise,

for example in increments of from about 0,1 to about 0,01 for the efficiency K/V.

Another approach is to use an exponential declination of the efficiency as outlined in Fig. 2.

The urea monitor concentration values may be used for controlling the efficiency. From the start, the highest possible efficiency is allowed. When the concentration value at the urea monitor reaches a low value, indicative of approaching the characteristic curve, the efficiency is controlled so that the urea monitor concentration value follows a predetermined curve, such as the efficiency curve of Fig. 2.

Consequently, the dialysis efficiency is adapted to the patient and to the concentration gradient he can withstand over the brain barrier without breaking down. In this case, the concentration gradient is dependent on the start concentration of urea in the brain, which, however, is dependent on the urea generation rate between the dialysis sessions. If it is assumed that the urea generation rate is fairly constant, the predetermined low concentration value of the urea monitor can be calculated in relation to the urea generation rate.

It is believed that the reason for reaching a time limit is the fact that the urea in the body is distributed between different compartments, for example extracellular and intracellular compartments. Urea in the extracellular compartment is readily available for dialysis by the high efficient dialysis process. When the urea in the extracellular compartment has been rapidly removed, the urea concentration in the blood will be low. Consequently, there is a high concentration gradient over those membranes, which do not readily pass the urea molecule, such as the brain barrier. Such high gradients are known to trigger the disequilibrium syndrome. Moreover, such high gradients will cause water to pass the brain barrier in the opposite direction, increasing the intracranial pressure, which may induce the disequilibrium syndrome.

If a higher efficiency is used from the start, the extracellular compartment will be depleted faster without allowing the intracellular compartment a sufficient time to give off any appreciable amount of urea. On the other hand, if a lower efficiency is used from the start, the patient can withstand the dialysis for longer time, since the intracellular compartment has time to contribute to the urea in the blood. This suggests why increased efficiency cannot be tolerated for a long time.

While this is a plausible explanation, we do not want to bind ourselves to this explanation, since there are plenty other factors contributing to the removal of urea. Moreover, urea is only one of the molecules removed during a dialysis session, and it cannot be ruled out that other molecules play an important role for the disequilibrium syndrome. Urea is commonly used as a marker molecule for dialysis efficiency.

The dialysis efficiency can be influenced upon in several ways. The most convenient is to change the blood flow rate, which has a direct, although unlinear relationship to the efficiency. It is also possible to change the dialysis fluid flow rate, which gives approximately the same results, or both. The same applies to hemofiltration and hemodiafiltration.

The dialysis efficiency is obtained by monitoring the urea concentration in the outgoing dialysis fluid flow. A typical urea concentration curve is shown in Fig. 3. The slope of the logarithm of the curve corresponds in principle to the efficiency K/V.

A typical dialysis machine is schematically shown in Fig. 4. The dialysis machine 1 comprises a dialysis fluid preparation portion 2 and a blood flow portion 3.

The blood flow portion 3 comprises a pump 4 propelling the blood in the extracorporeal blood circuit 5.

The dialysis fluid preparation portion 2 includes pumps 6, 7 which control the fluid flow rate of the dialysis fluid as well as ultrafiltration pressure applied across a

membrane 8 of a dialyzer 9. Two fluid flow meters 10, 11 determine the dialysis fluid flow rate as well as ultrafiltration flow obtained from the blood.

A urea monitor 12 is included in an outlet line 13 from the dialysis machine. The urea monitor is disclosed in details in WO 96/04401, which is incorporated by reference in this specification. The urea monitor 12 accurately determines the urea concentration in the outlet dialysis fluid line 13.

All signals from the flow meters 10, 11 pumps 4, 6, 7 and urea monitor 12 are fed to a computer 14.

The urea removal rate from blood is equal to the concentration times the dialysis fluid flow, since no urea is included in the incoming dialysis fluid. The total removed urea (TRU) is determined automatically by the urea monitor on a continuous basis.

When performing the method according to the present invention, the urea concentration values obtained by the urea monitor is used for determining the initial efficiency K/V of the dialyzer of the dialysis treatment. This requires that the urea monitor will be connected for a sufficient time so that a sufficient number of data has been collected. Usually, the efficiency is higher during the first 20 - 30 minutes and then declines to a more constant value. Consequently, it is often desired to wait for more than 30 minutes before determining the initial or actual efficiency.

When the actual efficiency of a specific dialysis session has been established, it can be assumed that the efficiency is approximately constant if no other factors are altered. In reality, there is a small decrease in the efficiency over time, but it is neglected for the purpose of the present explanation. Of course, the computer of the dialysis machine can be programmed to take account of such known variations.

After determining that the limit value has been reached by any of the above-mentioned methods, the computer 14 of the dialysis machine is programmed to change the efficiency,

usually by decreasing it. The relationship between the blood flow and the efficiency for a specific dialyzer can be included in the memory of the computer 14 and the computer can be programmed to change the efficiency as required, for example stepwise or continuously according to an exponential curve.

The urea monitor is used for determining the new efficiency after each alteration, and the efficiency values are integrated over time to indicate when a desired dose (Kt/V) of dialysis has been reached, whereupon the dialysis session may be ended. Of course other methods of determining when the dialysis session should be ended may be used, such as manual or time controlled ending.

The same profiling method can also be used for hemodiafiltration and hemofiltration.

Fig. 5 shows an embodiment intended for hemodiafiltration. All components which are equal to the components of the hemodialysis machine 1 shown in Fig. 4 has the same reference numerals as in Fig. 4.

In order to obtain the hemodiafiltration machine 15 of Fig. 5, essentially only a line 16 is added to the hemodialysis machine of Fig. 4, connecting the outlet of flow meter 10 to the extracorporeal circuit 5 for introducing a replacement fluid into the patient. The line 16 also comprises a pump 17 for controlling the amount of replacement fluid introduced into the patient via the extracorporeal circuit 5. Of course, the replacement fluid should be sterile.

The amount of ultrafiltration is still controlled by the pumps 6 and 7 as measured by flow meters 10 and 11. The volume of the replacement fluid introduced by pump 17 must be removed from the blood in the dialyzer, thereby increasing the filtration.

According to the present invention, the efficiency of the treatment should be varied, usually decreased during the treatment. Such decrease can be obtained by decreasing the blood flow in the hemodiafiltration machine 15 disclosed in Fig. 5. Another way of decreasing the efficiency would be to

decrease the replacement fluid flow, until, ultimately, the treatment is converted to hemodialysis when the replacement fluid flow is zero.

Another embodiment of the invention is disclosed in Fig. 6, which shows a hemofiltration machine 18. Some of the components are the same as in the embodiment of Fig. 4 and have the same reference numerals. However, the dialyzer 9 has no inlet line for dialysis fluid, but the line is replaced with a replacement fluid line 19 comprising a pump 20, a flow meter 21 and a line 22 for connection to the extracorporeal circuit 5 for introducing the replacement fluid into the blood of the patient. Fig. 6 shows postdilution where the replacement fluid is introduced after the dialyzer, but also predilution may be used, where the replacement fluid is introduced into the extracorporeal circuit 5 before the dialyzer.

According to the present invention, the efficiency of the treatment is varied or decreased by decreasing the replacement fluid flow and/or the blood flow. The ultrafiltration is maintained constant by the machine by means of the computer 14 calculating the difference between the flow meters 11 and 21 and controlling the pumps 7 and 20 in dependence of the measured values.

Another embodiment of a hemofiltration machine 23 is shown in Fig. 7. A portion of the inlet dialysis fluid is transferred to the outlet line 13 via a short-circuit line 24. Another portion of the dialysis fluid is taken out via line 25 to form a replacement fluid metered via a pump 26. The portions are known to computer 14 via flow meters 10 and 11 and the speed of pump 26.

According to the invention, the efficiency of the treatment is varied or decreased by decreasing the speed of pump 26 and/or decreasing the speed of pump 4.

As indicated above, other factors influence upon the dialysis treatment, and specifically water removal or ultrafiltration. A high ultrafiltration can result in intradialytic symptoms, most commonly symptomatic hypotension.

However, it has been found that profiling of the efficiency will also improve the patients resistance against symptomatic hypotension induce by high ultrafiltration during hemodialysis or hemofiltration.

Herein certain embodiments of the invention have been described. It is clear to the skilled person that the present invention can be modified and adapted to different dialysis machines and urea monitors within the scope of the invention. For example, other marker molecules than urea, such as creatinine, can be used for the purpose of this invention, whereby the urea monitor is replaced by a creatinine monitor. The invention can also be adapted to peritoneal dialysis.

Of course such modifications and alterations should be considered to be within the scope of the invention, which is only limited by the appended patent claims.

CLAIMS

1. A method of profiling an efficiency of a dialysis and/or filtration blood treatment, **characterized** by

performing said treatment with a predetermined high efficiency until a predetermined limit value has been reached;

changing the efficiency of said treatment according to a predetermined profile of efficiency; and

ending said treatment after reaching a predetermined dose of dialysis.

2. Method according to claim 1, **characterized** by determining a characteristic curve of efficiency tolerated for a specific patient and determining said limit value when said characteristic curve has been reached.

3. Method according to claim 1, **characterized** by determining said limit value as a predetermined amount of urea removed, as measured by a continuous urea monitor.

4. Method according to claim 3, **characterized** by determining said amount of urea removed in dependence of the urea generation rate determined for said patient.

5. Method according to claim 4, **characterized** by determining said amount of urea removed (m_{urea}) as the product of: the urea generation rate (G); the time (t_{inter}) between the dialysis sessions; and a patient factor (F), i.e.
$m_{urea} = G \times t_{inter} \times F$.

6. Method according to claim 1, **characterized** by determining said limit value as a predetermined concentration value of urea, as measured by a continuous urea monitor.

7. Method according to any of the preceding claims, **characterized** by profiling the efficiency of the treatment by changing the blood flow or a dialysis fluid flow through a dialyzer.

8. Method according to claim 2, **characterized** by profiling the efficiency of the treatment stepwise or continuously according to a curve closely approaching said characteristic curve.

9. Method according to claim 6, **characterized** by profiling the efficiency of the treatment for maintaining the urea concentration of the dialysis outlet fluid according to a predetermined profile.

10. A system for profiling an efficiency of a dialysis and/or filtration blood treatment, comprising means for exposing a patient for said treatment, **characterized** by:

means for performing said treatment with a predetermined high efficiency until a predetermined limit value has been reached;

means for changing the efficiency of said treatment according to a profile of efficiency; and

means for ending the treatment after reaching a predetermined dose of dialysis.

11. System according to claim 10, **characterized** by means for determining a characteristic curve of efficiency tolerated for a specific patient and means for determining said limit value when said characteristic curve has been reached.

12. System according to claim 10, **characterized** by means for determining said limit value as a predetermined amount of urea removed, as measured by a continuous urea monitor.

13. System according to claim 12, **characterized** by means for determining said amount of urea removed in dependence of the urea generation rate determined for said patient.

14. System according to claim 13, **characterized** by means for determining said amount of urea removed as the product of: the urea generation rate (G); the time (t_{inter}) between the dialysis sessions; and a patient factor (F), i.e. $m_{urea} = G \times t_{inter} \times F$.

15. System according to claim 10, **characterized** by means for determining said limit value as a predetermined concentration value of urea, as measured by a continuous urea monitor.

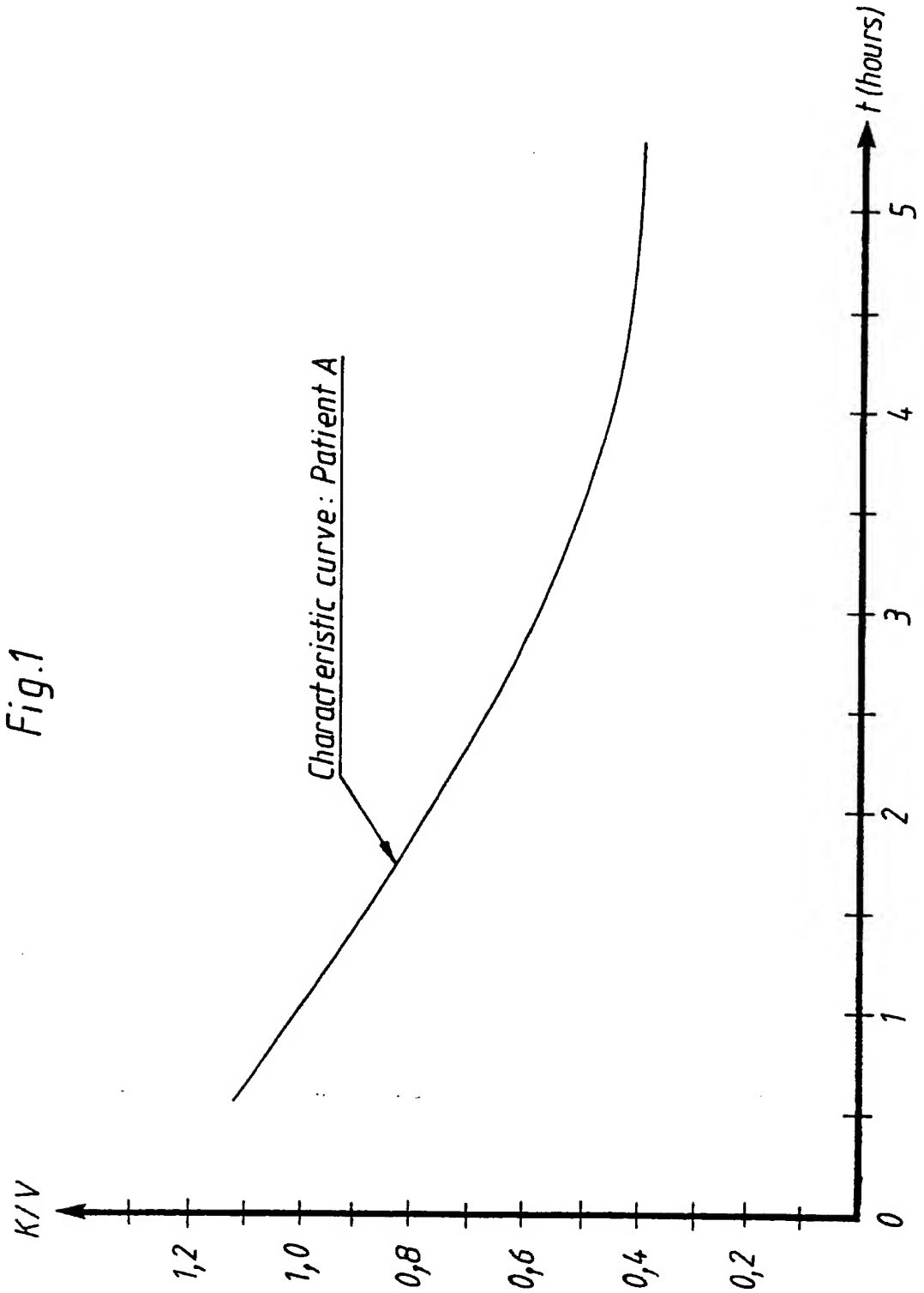
16. System according to any of claims 10 - 15, **characterized** by means for profiling the efficiency of the treatment, comprising means for changing the blood flow or a dialysis fluid flow through a dialyzer.

17. System according to claim 11, **characterized** by means for profiling the efficiency of the treatment stepwise or continuously according to a curve closely approaching said characteristic curve.

18. System according to claim 15, **characterized** by means for profiling the efficiency of the treatment for maintaining the urea concentration of the dialysis outlet fluid according to a predetermined profile.

19. System according to any of claims 10 - 18, **characterized** by the fact that said treatment is hemodialysis, hemofiltration or hemodiafiltration.

Fig.1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K/V
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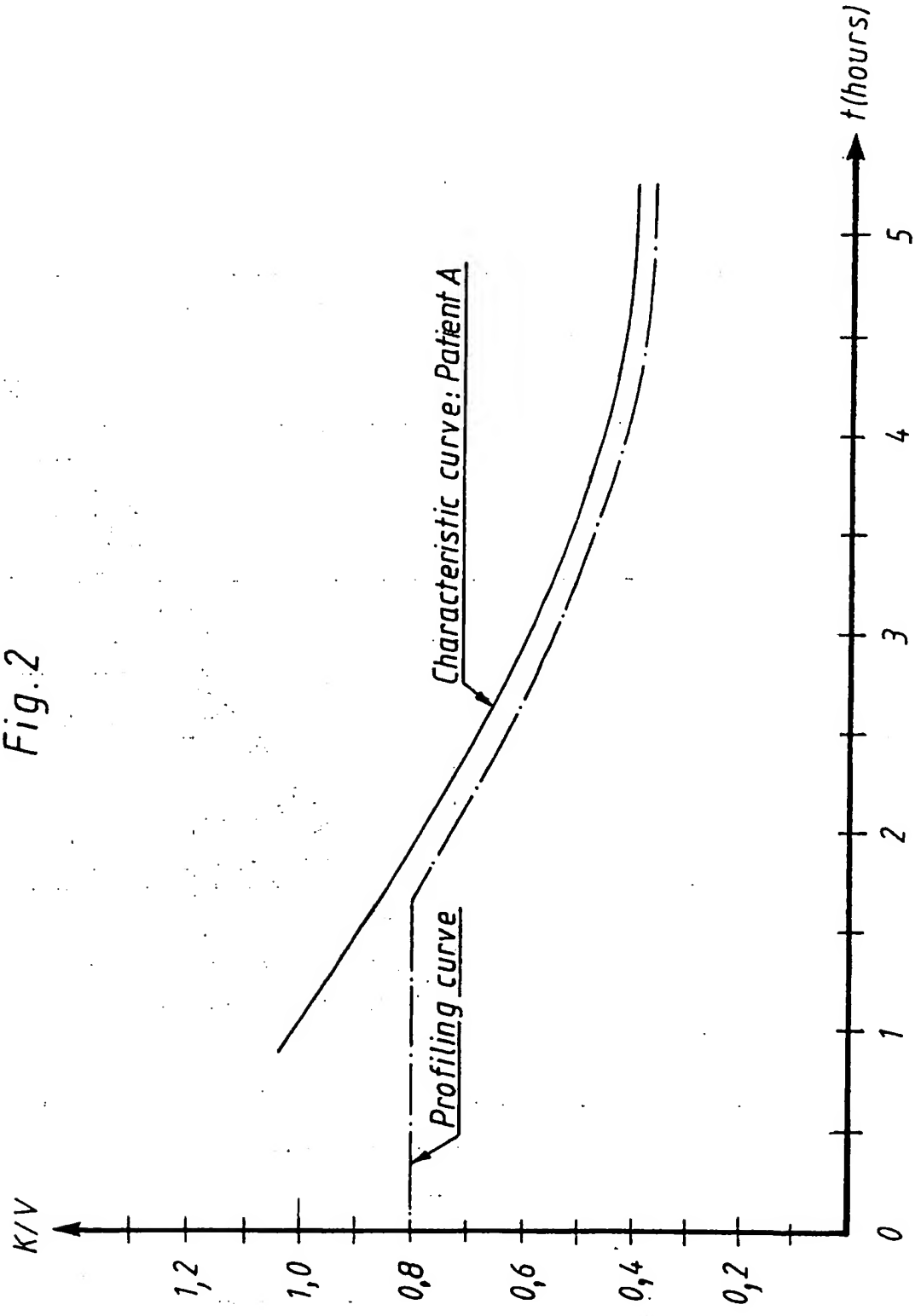
0,2
Characteristic curve: Patient A

Fig.2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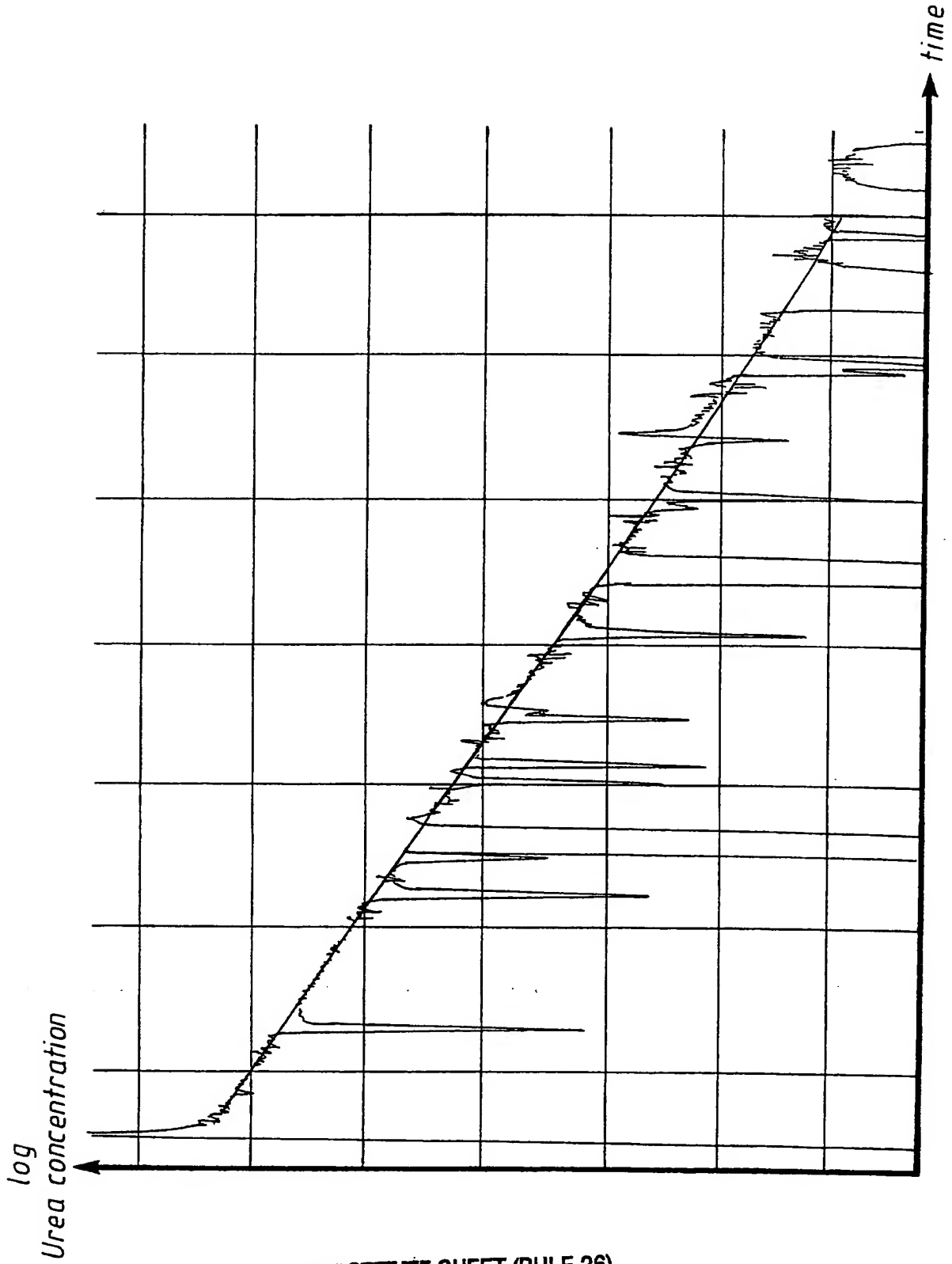
Characteristic curve: Patient A
Profiling curve

Fig. 3



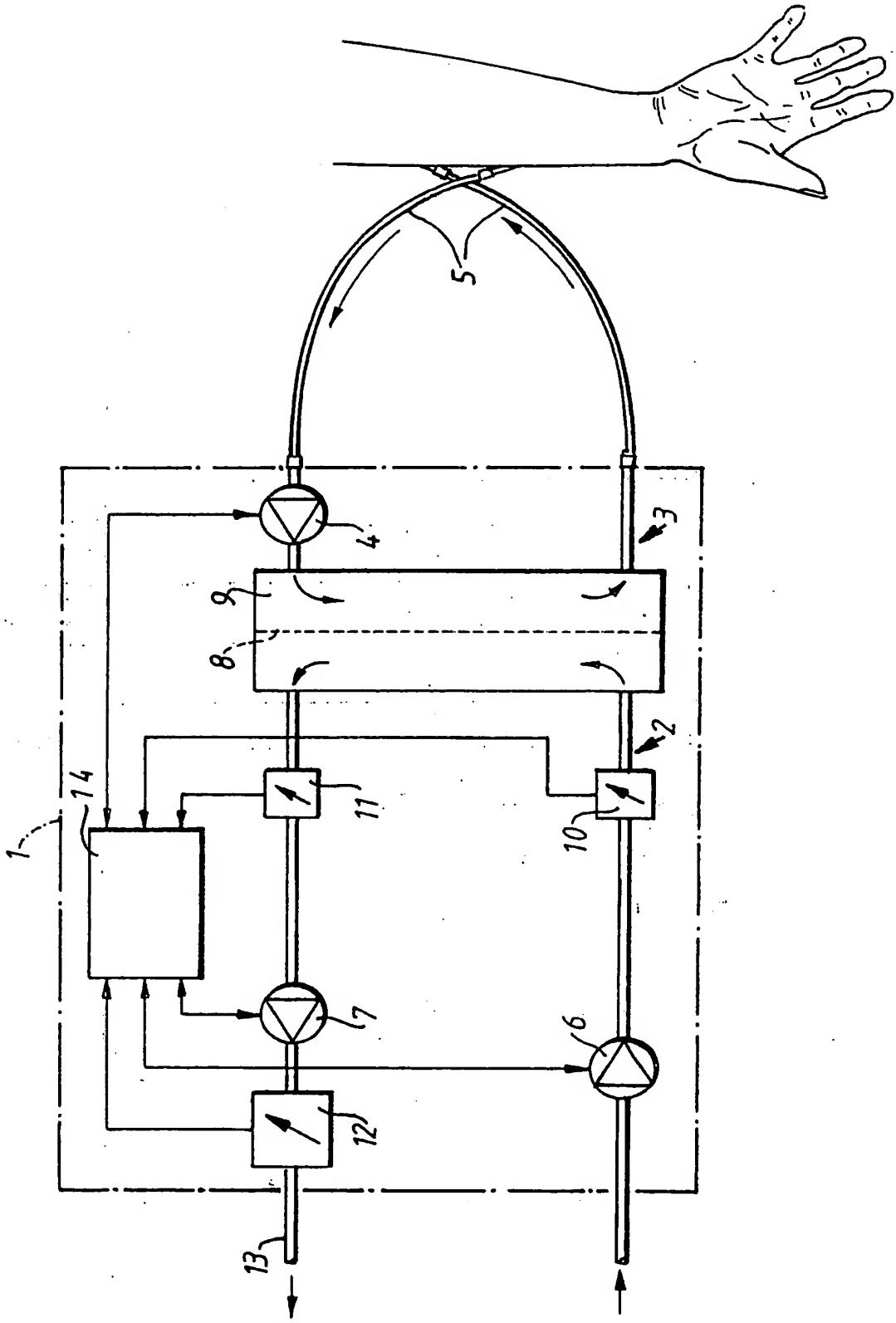


Fig. 4

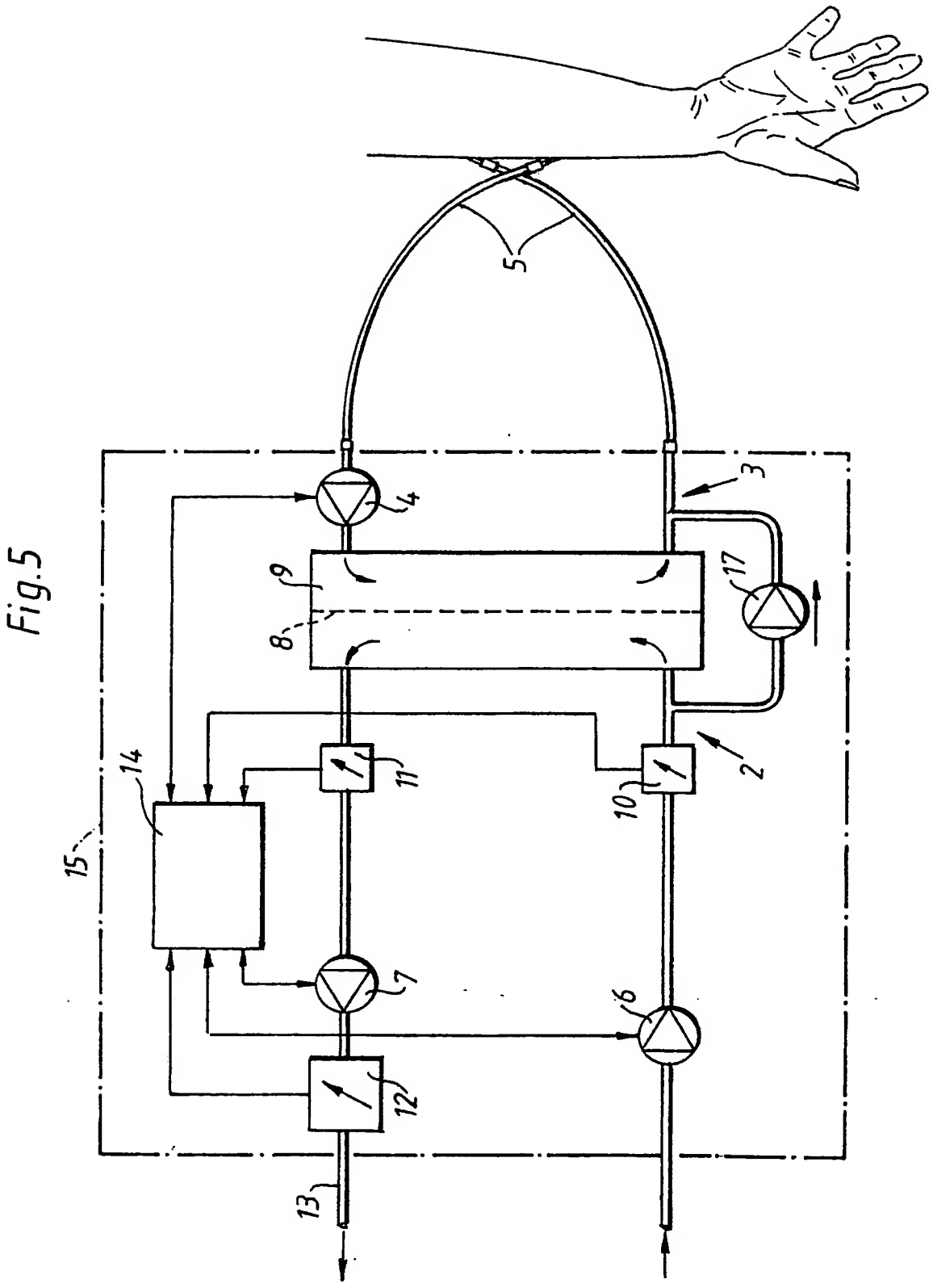
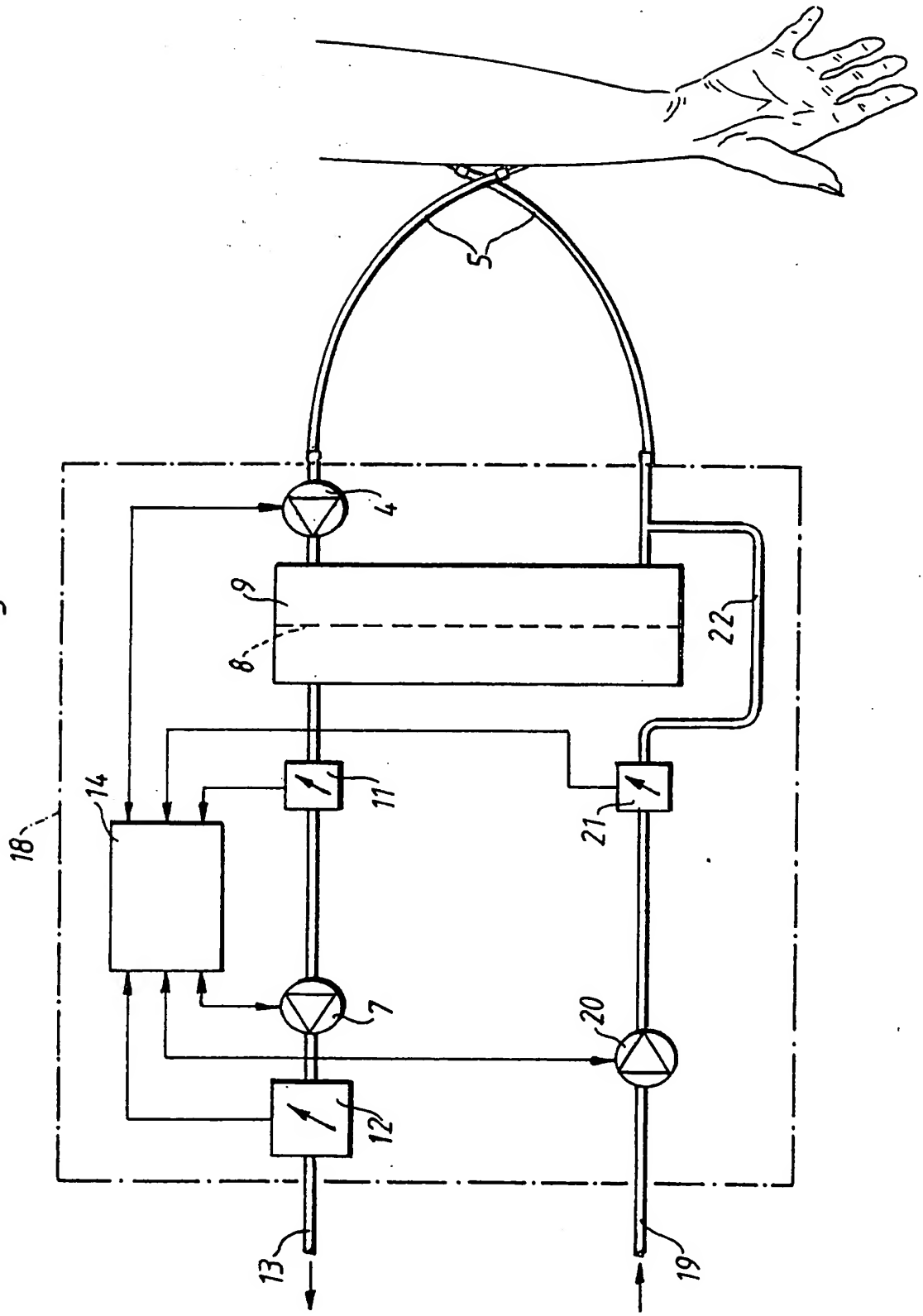


Fig.5

Fig. 6



INTERNATIONAL SEARCH REPORT

Information on patent family members

03/02/98

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